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C7 β -Methyl Analogues of the Orvinols: The Discovery of Kappa Opioid Antagonists with Nociceptin/Orphanin FQ Peptide (NOP) Receptor Partial Agonism and Low, or Zero, Efficacy at Mu Opioid Receptors

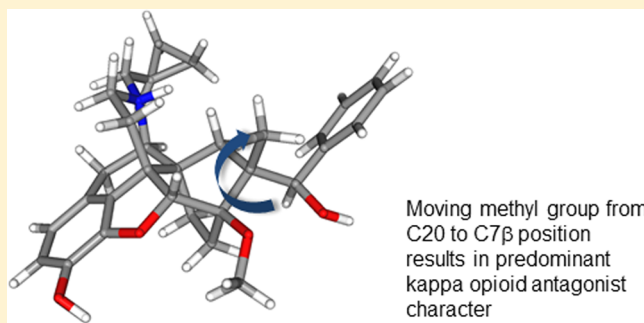
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S Supporting Information

ABSTRACT: Buprenorphine is a successful analgesic and treatment for opioid abuse, with both activities relying on its partial agonist activity at mu opioid receptors. However, there is substantial interest in its activities at the kappa opioid and nociceptin/orphanin FQ peptide receptors. This has led to an interest in developing compounds with a buprenorphine-like pharmacological profile but with lower efficacy at mu opioid receptors. The present article describes aryl ring analogues of buprenorphine in which the standard C20-methyl group has been moved to the C7 β position, resulting in ligands with the desired profile. In particular, moving the methyl group has resulted in far more robust kappa opioid antagonist activity than seen in the standard orvinol series. Of the compounds synthesized, a number, including **15a**, have a profile of interest for the development of drug abuse relapse prevention therapies or antidepressants and others (e.g., **8c**), as analgesics with a reduced side-effect profile.



INTRODUCTION

Buprenorphine (**1a**, Chart 1) is widely used for the treatment of opioid abuse and as an analgesic. Its mu opioid receptor (MOPr) partial agonist character is of primary importance for both indications, but it is apparent that activity at other receptors, in particular, antagonism at the kappa opioid receptor (KOPr), may play an important role in its clinical utility.¹

The very high rate of relapse to drug use after a period of abstinence is a major problem in substance abuse treatment, with ~70% of treated addicts relapsing within the first year following treatment.² The fact that many drug users use more than one drug further complicates the situation. A variety of factors play a role in precipitating relapse, but stress and/or a priming dose of the drug are particular risks. In preclinical studies, inhibition or genetic ablation of KOPrs has been shown to inhibit stress-induced relapse, but this approach has not been effective in blocking drug-prime-induced reinstatement to drug-seeking behavior.³

In contrast to the studies using selective KOPr antagonists, our own preclinical findings^{4,5} suggest that a combination of buprenorphine and naltrexone can be effective in blocking drug-prime-induced reinstatement to both cocaine- and opioid-seeking behavior. The combination acts as a KOP and delta

opioid (DOP) receptor antagonist,⁶ a lower potency nociceptin/orphanin FQ peptide (NOP) receptor partial agonist,⁷ and a MOP antagonist.

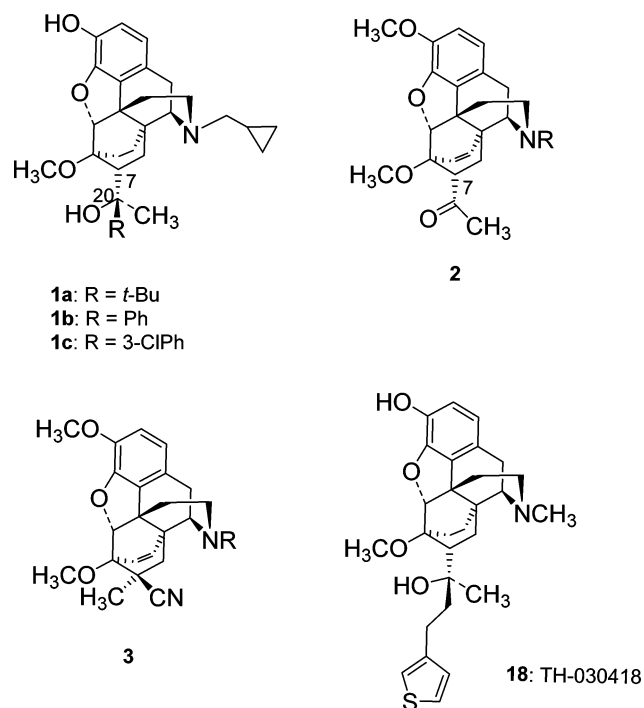
Encouraging results have also been observed in two small clinical trials using a buprenorphine and naltrexone combination therapy in a ratio that should block most, or all, of buprenorphine's MOPr agonist activity.^{8,9} The combination proved to be effective in reducing relapse in recovering opiate addicts and also caused a significant reduction in cocaine use. The beneficial effect on cocaine use is being more thoroughly evaluated within The National Drug Abuse Treatment Clinical Trials Network in the Cocaine Use Reduction with Buprenorphine (CURB: CTN-0048) study.

Thus, preclinical and clinical data suggest that the buprenorphine–naltrexone combination has significant therapeutic potential for the treatment of relapse and polydrug addiction, but it has substantial issues that need to be resolved. First, delivery of the combination is problematic; buprenorphine has poor oral bioavailability and is given sublingually, whereas naltrexone is active after oral administration but much less so after sublingual administration. The two compounds are

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Chart 1



therefore not amenable to formulation as a single tablet, and it is not desirable to use the two drugs separately due to potential compliance issues and the possibility of buprenorphine being diverted for illicit, nonmedical use. Second, the exact pharmacological profile provided by the combination is not clear, particularly whether there is a “pure” antagonist or a low-efficacy MOPr component. Provision of single chemical entities that provide buprenorphine-like activity at KOP, DOP, and NOP receptors but with substantially reduced efficacy at MOPr will allow these issues to be resolved and will provide compounds with potential therapeutic utility for relapse prevention and poly drug abuse.

Buprenorphine has also found widespread use as an analgesic and appears to be effective in neuropathic pain conditions that are not sensitive to other opioids, although the mechanism for this difference is not clear.¹⁰ There has been speculation that buprenorphine’s unique clinical profile might be linked to its ability to act as a low-efficacy partial agonist at NOPr in addition to its MOPr partial agonism,¹¹ although Cremeans et al. found no evidence for activation of NOPr being important for buprenorphine’s analgesic activity in primates.¹² On the other hand, they did find that coactivation of MOPr and NOPr produced synergistic antinociception. This suggests that bifunctional ligands with low efficacy at MOPr and moderate efficacy at NOPr might have utility as analgesics with a reduced side-effect profile. Efforts to develop such bifunctional ligands are being made.¹³

Orvinols, the series of compounds to which buprenorphine belongs, typically display high efficacy at one, or both, of the MOPr and KOPr.¹⁴ However, we recently reported on a series of aryl analogues of buprenorphine, some of which displayed substantially lower efficacy at the opioid receptors while retaining high affinity for opioid receptors and moderate (equivalent to buprenorphine) affinity for NOPr.¹⁵ We now report on a series of orvinol analogues in which the C20-methyl group has been moved to the C7- β position, resulting in more

robust KOPr antagonism, enhanced NOPr activity, and low-efficacy partial agonism, or antagonism, at MOPr. A number of the ligands can be considered as single compound alternatives to the buprenorphine/naltrexone combination, while others offer potential as analgesics with a reduced side-effect profile.

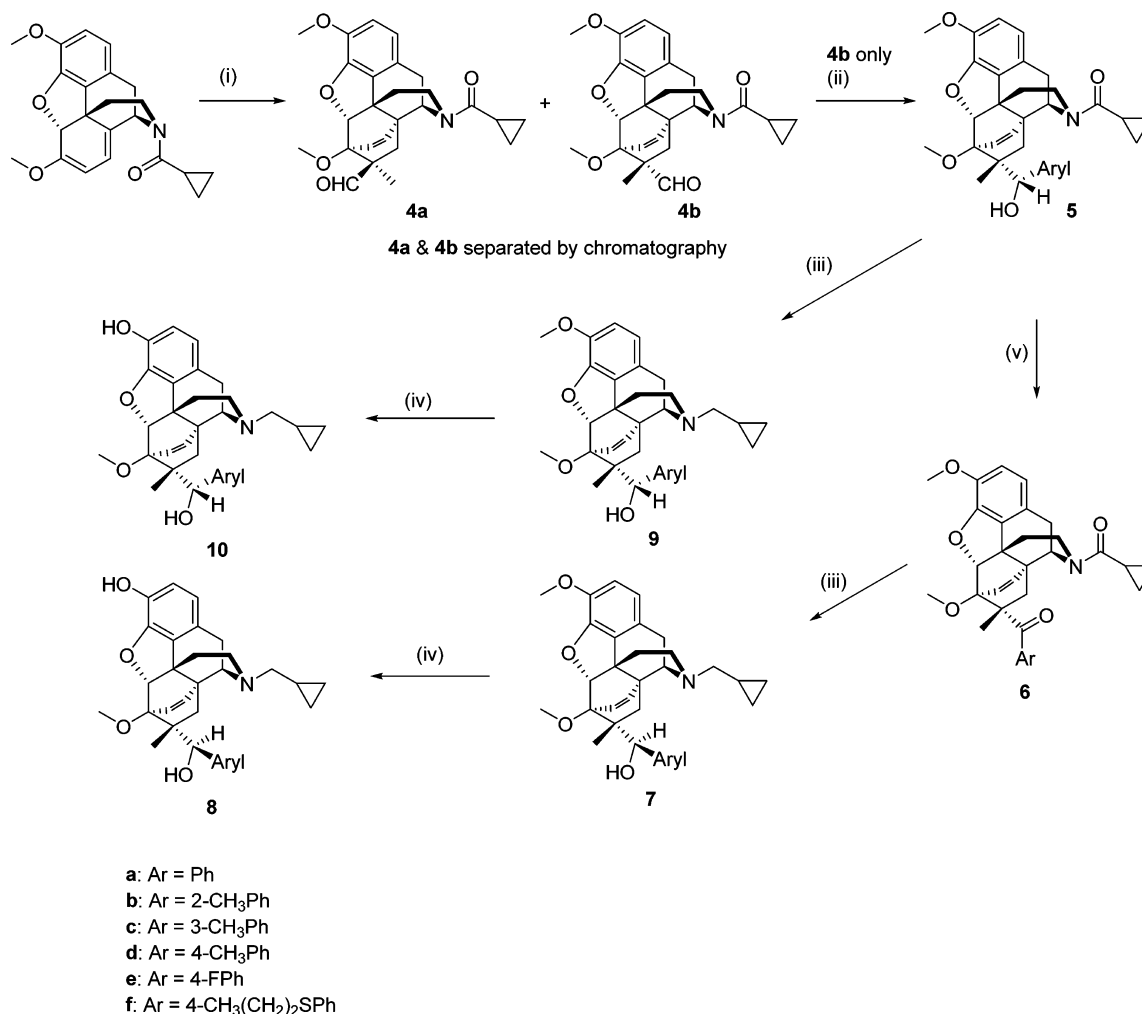
SYNTHESIS

In theory, a C7- β -methyl group could be introduced into orvinol type compounds by methylation of the keto-intermediate (2, Chart 1). In practice, this leads to a number of rearrangement products resulting from the instability of the C7-anion.^{16,17} The alternative approach is to introduce the methyl group during the Diels–Alder reaction. Methacrylonitrile is known to undergo the Diels–Alder reaction with thebaine and *N*-cyclopropylnorthebaine, but it gives the C7 α -methyl adduct (3, Chart 1), the opposite to that desired and a result of the methyl group being bulkier than the nitrile.¹⁸ Methacrolein should give a more favorable distribution of product due to the increased bulk of the aldehyde, but it has been reported that methacrolein does not undergo Diels–Alder reaction with thebaine.¹⁹ We have previously shown that lithium tetrafluoroborate catalyzes Diels–Alder reactions between *N*-cyclopropylcarbonylnorthebaine and cycloalkenones²⁰ and have now applied this method to the reaction with methacrolein (Scheme 1). The reaction was successful, giving a 1.4:1 mixture of the C7 α -methyl (4a) and C7 β -methyl (4b) adducts that could be separated by silica gel chromatography. Addition of phenyl Grignard, in the presence of tetrabutylammonium bromide, to 4b gave the secondary alcohol 5a, with opposite stereochemistry at C20 to that desired. This bias toward the *S*-isomer (5a) parallels our findings on Grignard addition to the aldehyde of the related C7 β -H series¹⁴ and is opposite to that observed on addition of Grignard reagent to the methyl ketone in the C7 β -H series.^{14,15} Treatment of 5a with LiAlH₄ to reduce the amide before 3-O-demethylation gave 10a. To obtain the desired diastereoisomer, 5a was oxidized to the phenyl ketone (6a) before LiAlH₄ reduction of both the cyclopropylcarbonyl group and the ketone, the latter occurring stereoselectively, to give 7a. 3-O-Demethylation yielded 8a. The analogues (8b–8e; 10b–10e) were prepared in an identical manner. The 4-fluoro analogues (7e, 9e) were not fully stable to propanethiolate-mediated 3-O-demethylation, which, in the case of 7e, resulted in the formation of isolable amounts of 8f where the fluoro substituent was substituted by propanethiol.

The etheno-bridged aldehyde 4b was also hydrogenated to 11, and the same sequence of steps was carried out to provide the ethano-bridged analogues 15 and 17 (Scheme 2).

RESULTS

In order to streamline the development process and avoid unnecessary full evaluation of ligands of limited interest to this project, the compounds were screened in a [³⁵S]GTP γ S assay for MOPr, KOPr, and NOPr efficacy at a very high concentration (10 μ M) to determine peak efficacy at each receptor (Table 1). Potencies as agonists (EC₅₀) or antagonists (K_e) were then determined for the most interesting compounds (chosen based on efficacies at the receptors and their fit with the target profiles) and reported in Table 1. A range of compounds were also evaluated for affinity at MOP, DOP, and KOP receptors by measuring displacement of [³H]-diprenorphine binding from membranes of C6-rat glioma

Scheme 1^a

^a(i) Methacrolein, LiBF₄; (ii) ArMgBr, Bu₄NBr, THF, reflux; (iii) LiAlH₄, THF; (iv) PrSnNa, HMPA; (v) DMSO, oxalyl chloride, CH₂Cl₂.

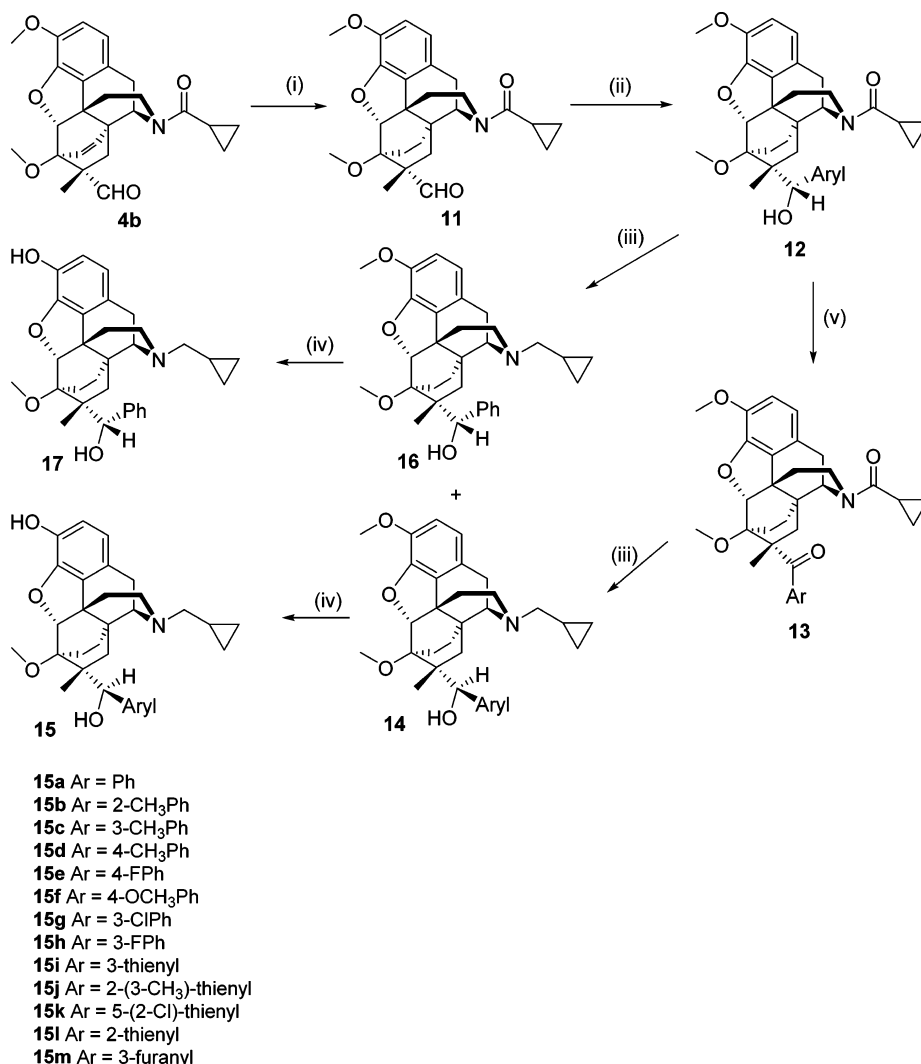
cells expressing recombinant rat MOPr and DOPr and CHO cells expressing recombinant human KOPr (Table 2). NOPr binding affinity was measured by displacement of [³H]-nociceptin from membranes of HEK cells expressing recombinant NOPr. Details of these assays have been described previously.^{6,21–24}

All ligands from series 8 are KOPr antagonists with maximal percent stimulation <10%. Efficacy at MOPr ranges from zero (8a) to moderate efficacy partial agonism (8d, 8f: 35 and 49% of DAMGO, respectively) with clear SAR relating to the location of the phenyl ring substituent (4' > 3' > 2'). At NOPr, the compounds were partial agonists somewhat similar in efficacy to buprenorphine, with the highest efficacy demonstrated by the unsubstituted (8a; 56%), 3'-methyl substituted (8c; 43%), and 4'-fluoro (8e, 51%) analogues. Potency at NOPr was higher than seen with buprenorphine. Series 10, the diastereomers of 8, were consistently of higher efficacy at the KOPr with only the 4'-Me (10d) substituted analogue profiling as a KOPr antagonist. The others in the series were moderate to high efficacy KOPr agonists (45–92% of U69,593). At MOPr, they were all of moderate efficacy (33–55%) and very low efficacy at NOPr.

The phenyl and substituted phenyl, ethano-bridge analogues (15a–h) had very similar SAR to series 8 in that they also had

very low, or no, efficacy at KOPr. A number (15a–e) were evaluated as antagonists at this receptor and were found to be as potent as buprenorphine (all having K_e < 1 nM). As with series 8, they were also antagonists (e.g., 15a) or low-efficacy partial agonists at MOPr (≤17% of DAMGO). While SAR at this receptor was not absolutely clear cut, 4'-substituents again gave rise to higher efficacy than 3'-substituents (e.g., 15e vs 15h, 15d vs 15c). This series was extended to include heterocyclic analogues 15i–15m. Those having a thiophene ring (15i–15l) had partial agonist activity at KOPr (10–28%) and at MOPr (10–61%), whereas 15m, having a 3-furanyl group, was devoid of efficacy at KOPr and MOPr. Only 15m had appreciable efficacy at NOPr within the series of heterocyclic analogues. 17, the C20-diastereoisomer of 15a, was a full agonist at KOPr (97% stim) and a partial agonist at MOPr, with little efficacy at NOPr.

Binding affinities were determined for a range of compounds, including the more interesting analogues from series 8 and 15. As would be expected, all had high affinity for MOPr and KOPr (and DOPr when tested) with subnanomolar K_i values. Of particular note was the range of affinities at NOPr, where a number of the compounds had substantially higher affinity than that of buprenorphine (e.g. 8e, 15d, 15e, 15f, 15k), whereas

Scheme 2^a

^a(i) H₂, Pd/C, EtOH; (ii) ArMgBr, Bu₄NBr, THF, reflux; (iii) LiAlH₄, THF; (iv) PrSnNa, HMPA; (v) DMSO, oxalyl chloride, CH₂Cl₂.

others had roughly equivalent affinity to that of buprenorphine (e.g., **8a**, **8c**, **15a**, **15b**, **15c**).

In order to help explain the unusually low efficacy at KOPr of this series, the docking of **15a** to the crystal structure of the KOPr was examined. The crystal structure of the KOPr was determined in the presence of the selective KOPr antagonist JD₇Tic and presumably represents the inactive conformation of the receptor and, importantly, the conformation favored when binding **15a**.²⁵ **15a** sits in the hydrophobic binding pocket with the expected interaction between the protonated nitrogen and the side chain of Asp138, while the C7β-methyl projects toward Tyr139 in TM3 (Figure 1).

DISCUSSION

Members of the orvinol series of compounds are mostly known for their nonselective binding to MOPr, KOPr, and DOPr and potent agonist activity at one or more of these receptors.²⁶ Even those with a cyclopropylmethyl (CPM) group attached to the basic nitrogen, which has the effect of reducing efficacy particularly at MOPr,²⁷ tend to be efficacious and potent agonists, primarily at KOPr.¹⁴ Buprenorphine, being a KOPr antagonist, is a very distinct member of the series, with the lack

of efficacy at KOPr being attributed to the significant steric bulk adjacent to C20.¹⁴ Initially, it was believed that buprenorphine was also unusual in having measurable affinity for NOPr,²⁸ an activity that has been postulated to explain some of buprenorphine's in vivo pharmacology.^{29,30} However, in recent years, it has become apparent that some other members of the orvinol family also interact with NOPr, particularly those with a bulky group attached to C20 (the *t*-butyl group of buprenorphine fulfills this role).^{31–33} While it has been possible to introduce good affinity for NOPr, it has proven to be difficult to couple this with moderate efficacy for this receptor without also introducing efficacy for classical opioid receptors, in particular KOPr. The orvinol TH-030418 (**18**; Chart 1) is reported as having affinity for NOPr virtually equivalent to its affinity for MOPr, KOPr, and DOPr; however, it also displays very potent and efficacious antinociceptive activity in vivo. This activity is blocked by the opioid antagonist naloxone, indicating high efficacy at MOPr and/or KOPr.³³ Even more closely related to the current series are analogues of **1a** having alternative bulky groups at C20.³¹ In that series, moderate affinity and efficacy for NOPr was always associated with partial agonism at MOPr and/or KOPr. The robust KOPr antagonist activity of series **8** and **15**, especially when coupled with

Table 1. Maximal Stimulation of [³⁵S]GTPγS Binding of the New C7β-Methyl Orvinol Analogues to Opioid and NOP Receptors

	[³⁵ S]GTPγS, % stimulation, ^a and, in brackets, agonist EC ₅₀ /nM or antagonist K _e /nM ^b			
	MOPr	KOPr	NOPr	DOPr
1a	20 ± 6% (EC ₅₀ : 0.7 ± 0.3nM)	0 ± 6% (K _e = 0.14 ± 0.06 nM)	39 ± 12% (EC ₅₀ : 1480 ± 980 nM)	7 ± 3%
1b	6.0 ± 1	19 ± 4	14 ± 4	
8a	4 ± 6%	3 ± 7%	56 ± 2.5% (EC ₅₀ : 416 ± 74 nM)	7 ± 3%
8b	12 ± 5%	−4 ± 1%	17 ± 1%	
8c	22 ± 5% (EC ₅₀ : 1.4 ± 0.4 nM)	6 ± 2%	54 ± 11% (EC ₅₀ : 14 ± 5 nM)	15 ± 3%
8d	35 ± 11% (EC ₅₀ : 0.24 ± 0.04 nM)	−6 ± 1%	14 ± 2%	
8e	26 ± 8% (EC ₅₀ : 0.22 ± 0.06 nM)	9 ± 1%	51 ± 20% (EC ₅₀ : 7.3 ± 3 nM)	
8f	49 ± 2%	4 ± 10%	20 ± 4%	
10a	33 ± 6%	62 ± 4%	5 ± 6%	
10b	48 ± 1%	72 ± 4%	12 ± 2%	
10c	40 ± 13%	92 ± 4%	11 ± 3%	
10d	49 ± 3%	8 ± 5%	4 ± 5%	
10e	55 ± 7%	45 ± 6%	7 ± 3%	
15a	2 ± 4% (K _e = 0.28 ± 0.04 nM)	−2 ± 1% (K _e = 0.09 ± 0.04 nM)	56 ± 1% (EC ₅₀ : 147 ± 33 nM)	0 ± 4%
15b	15 ± 7%	−4 ± 4% (K _e = 0.13 ± 0.05 nM)	15 ± 4%	
15c	7 ± 1%	−1 ± 1% (K _e = 0.12 ± 0.08 nM)	61 ± 15% (EC ₅₀ : 331 ± 223 nM)	
15d	14 ± 4%	−5 ± 4% (K _e = 0.10 ± 0.05nM)	4 ± 3%	
15e	17 ± 2%	−5 ± 3% (K _e = 0.10 ± 0.05 nM)	13 ± 5%	6 ± 3%
15f	15 ± 1%	2 ± 1%	3 ± 1%	
15g	7 ± 1%	7 ± 4%	42 ± 3% (EC ₅₀ : 230 ± 37 nM)	
15h	2 ± 1%	15 ± 4%	31 ± 2% (EC ₅₀ : 160 ± 70 nM)	
15i	10 ± 1	28 ± 6	2 ± 1	
15j	31 ± 4	26 ± 2	15 ± 1	
15k	61 ± 2%	10 ± 2%	16 ± 3%	
15l	10 ± 4%	20 ± 2%	6 ± 3%	
15m	1 ± 1%	2 ± 4%	29 ± 3% (EC ₅₀ : 230 ± 70 nM)	
17	33 ± 7%	97 ± 5%	10 ± 4%	

^aPercent maximal stimulation (% stim) at a single high concentration (10 μM) with respect to the standard agonists DAMGO (MOPr) and U69,593 (KOPr) and nociceptin (NOPr); values are an average ± SEM from three separate experiments. ^bIn brackets for selected compounds, agonist EC₅₀/nM or antagonist K_e (the antagonist dissociation constant determined against the standard agonists listed above) are given.

improved affinity for NOPr, is therefore unprecedented within the orvinols and close analogues. That they are 2° alcohols, which typically have very much higher efficacy than their 3° analogues,¹⁴ confirms the very substantial effect of moving the methyl group from C20 to the C7β-position. A comparison with the recently reported **1b** and aryl substituted analogues confirms the importance of this methyl group. **1b** and analogues differ from **15** only in the location of this single methyl, yet in the **1b** series, only the parent compound (R = Ph) and the 3'-chloro analogue (**1c**: R = 3-ClPh) had low efficacy at KOPr (19 and 26%, respectively), with other substituents (2'-, 3'-, and 4'-methyl, 3'- and 4'-F) all resulting in efficacy in the range 77–102% at this receptor.¹⁵

Docking of **15a** to the published crystal structure of the KOPr²⁵ allows a hypothesis to be formulated to explain the very low efficacy of this series to the KOPr. In the model of the KOPr active and inactive states,²³ the methyl group of **15a** projects toward Tyr139 in TM3. In the inactive conformation, Tyr139 and the whole of TM3 move away from this position, whereas in the active conformation, they are much closer, possibly too close to allow the active conformation to be taken up; i.e., through an interaction between the C7β-methyl group and Tyr139, **15a** and analogues may disfavor the active state of the receptor.

Distinct SAR for affinity and efficacy at NOPr is found in series **8** and **15**. In both cases, the unsubstituted parent or a 3'-substituent gives highest efficacy at NOPr, whereas highest affinity is associated with a 4'-substituent, although this latter effect is not large.

CONCLUSIONS

Moving the methyl group from C20 to the C7β position has resulted in one of the most striking pieces of SAR in the orvinol series. In particular, the robust reduction in efficacy at KOPr coupled with a retention, or increase, in NOPr affinity and efficacy has resulted in a series of compounds worthy of consideration as (i) relapse prevention agents and (ii) low abuse liability analgesics. **15a** is currently undergoing in vivo evaluation as part of its preclinical development.

EXPERIMENTAL SECTION

General Procedures. Reagents and solvents were purchased from Sigma-Aldrich or Alfa Aesar and used as received. Buprenorphine (**1a**) was supplied by the National Institute on Drug Abuse, Bethesda, Maryland. ¹H and ¹³C NMR spectra were obtained with a Bruker 400 MHz instrument (¹H at 400 MHz, ¹³C at 100 MHz); δ is given in ppm, J, in Hz, with TMS as an internal standard. ESIMS: microTOF (BRUKER), EIMS: Fisons Autosampler. Microanalysis: PerkinElmer

Table 2. Binding Affinities (K_i /nM) of of the New C7 β -Methyl Orvinol Analogues to Opioid and NOP Receptors

	binding/nM ^a			
	MOPr	KOPr	NOPr	DOPr
1a	0.13 \pm 0.02	0.089 \pm 0.02	212 \pm 7	0.48 \pm 0.26
1b	0.17 \pm 0.05	0.044 \pm 0.015	43.2 \pm 13.4	NT
8a	0.08 \pm 0.02	0.08 \pm 0.03	97 \pm 12	0.48 \pm 0.05
8b	NT	NT	1270 \pm 170	NT
8c	0.17 \pm 0.11	0.04 \pm 0.01	79 \pm 8	0.40 \pm 0.16
8e	0.16 \pm 0.12	0.05 \pm 0.01	34 \pm 6	NT
15a	0.10 \pm 0.02	0.04 \pm 0.01	80 \pm 10	0.25 \pm 0.18
15b	0.20 \pm 0.07	0.12 \pm 0.03	820 \pm 60	NT
15c	0.098 \pm 0.022	0.11 \pm 0.04	240 \pm 50	NT
15d	0.14 \pm 0.06	0.16 \pm 0.05	56 \pm 5	NT
15e	0.071 \pm 0.014	0.10 \pm 0.03	56 \pm 3	0.47 \pm 0.38
15f	NT	NT	26 \pm 6	NT
15g	0.052 \pm 0.007	0.094 \pm 0.04	47.8 \pm 17	NT
15h	0.09 \pm 0.03	0.13 \pm 0.05	62.2 \pm 31	NT
15k	NT	NT	44 \pm 11	NT
15l	NT	NT	571 \pm 77	NT
15m	0.11 \pm 0.011	0.14 \pm 0.10	1455 \pm 469	NT

^a K_i (nM) versus [³H]diprenorphine (for MOPr, KOPr, and DOPr) and [³H]nociceptin (for NOPr); values are an average \pm SEM from three separate experiments. NT: not tested

240C analyzer. Column chromatography was performed using RediSep prepac columns with a Teledyne Isco CombiFlash instrument. Most ligands were tested as their hydrochloride salts, prepared by adding 5 equiv of HCl (1 N solution in diethyl ether) to a solution of compound in anhydrous methanol. Alternatively, the oxalate salt was formed by adding 1 equiv of oxalic acid in EtOH to the ligand in EtOH. All reactions were carried out under an inert atmosphere of nitrogen unless otherwise indicated. All compounds were >95% pure, as determined by microanalysis. A representative synthesis is reported here.

Arylmagnesium Halide Addition (General Procedure A). To a solution of aldehyde **4b** or **11** in dry THF (10 mL/mmol of aldehyde) were added 3 equiv of Bu₄NBr followed by 2 equiv of arylmagnesium halide as solution in THF. The solution was then heated at reflux for 48 h, cooled to RT, and quenched with 0.05 mL of water. The mixture was allowed to stir for 5 min and then filtered over Celite. The solids were washed with hot THF, and the solution was removed of its solvent by rotary evaporation. The remaining residue was partitioned between EtOAc (20 mL) and water (10 mL). The aqueous layer was extracted twice with 5 mL of EtOAc. The pooled organic solvent was washed twice with water (5 mL) and once with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The residue was dissolved in a minimum amount of Et₂O to

induce crystallization. The crystals were collected by filtration and dried under vacuum.

Swern Oxidation/LiAlH₄ Reduction of Secondary Alcohols (General Procedure B). A solution of oxalyl chloride (1.25 equiv) in CH₂Cl₂ (3 mL/mmol) was cooled to -78°C in a one-necked flask. Into this flask was added dropwise a solution of dry DMSO (2.6 equiv) in CH₂Cl₂ (3 mL/mmol). The solution stirred for 5 min, and then a solution of thevinol **5** or **12** in CH₂Cl₂ (2 mL/mmol) was added. The mixture stirred for 20 min, and then Et₃N (5 equiv) was added. The reaction was removed from the cold bath and stirred for 1 h, and water was added. The mixture was shaken, and the organic layer was separated and washed with a saturated solution of NH₄Cl and then with a concentrated solution of NaHCO₃. The solution was washed once more with brine, dried over magnesium sulfate, and filtered, and the solvents were removed under reduced pressure to yield crude **6** or **13** as a clear solid.

This residue was dissolved in dry THF (10 mL/mmol) and added to a stirring suspension of LiAlH₄ (4 equiv) in dry THF (5 mL/mmol) at 0°C . The suspension was allowed to warm to RT and was stirred for 24 h. The reaction was cooled to 0°C and quenched with water in THF. The mixture was filtered, rinsing the solids with hot THF. The solution was subjected to rotary evaporation to yield an oil that was subjected to silica gel column chromatography, eluting with 15% EtOAc in petroleum ether to yield two constituents, **7** or **14** (as the major product), as a high R_f component, and **9** or **16** (as the minor product), with lower R_f .

O-Demethylation Using NaSPr/HMPA (General Procedure C). A solution of thevinol **7**, **9**, **14**, or **16** in dry HMPA (6 mL/mmol) was added sodium propanethiolate (6 equiv). The reaction was stirred for 3 h at 115°C and then cooled to RT and quenched with 7 mL/mmol of a concentrated solution of NH₄Cl. The mixture was extracted three times with Et₂O. The organic layer was then extracted five times with water and once with brine, dried over MgSO₄, and filtered, and the solvents were removed under reduced pressure. The residue was then subjected to silica gel flash column chromatography, eluting with a gradient of EtOAc in petroleum ether. The fractions containing the compound of interest were then evaporated to dryness, dissolved in a 2 M solution of HCl in EtOH, and then induced to crystallize upon addition of EtOAc. The crystals were collected by filtration and dried under vacuum.

N-Cyclopropylcarbonyl-7 α -formyl-7 β -methyl-6,14-endo-ethenotetrahydronorthebaine (4b**).** To a suspension of 13.61 g (37.29 mmol) N-CPCnorthebaine in 20 mL of methacrolein was added 3.49 g of LiBF₄. The resulting solution was stirred for 16 h at RT. Into this solution was added 30 mL of CH₂Cl₂, and the mixture was extracted with water (10 mL \times 3) and brine (5 mL). The solution was dried, filtered, and removed of solvent on a rotary evaporator to afford a dark red syrup. This material was subjected to silica gel flash column chromatography, eluting with 50% EtOAc in petroleum ether to afford 5.91 g of the faster running component **4a** (N-cyclopropylcarbonyl-7 β -formyl-7 α -methyl-6,14-endo-ethenotetrahydronorthebaine) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.85 (s, 1H), 6.67 (d, 1H, J = 8.0 Hz), 6.57 (d, 1H, J = 8.0 Hz), 6.14–6.07 (2d,

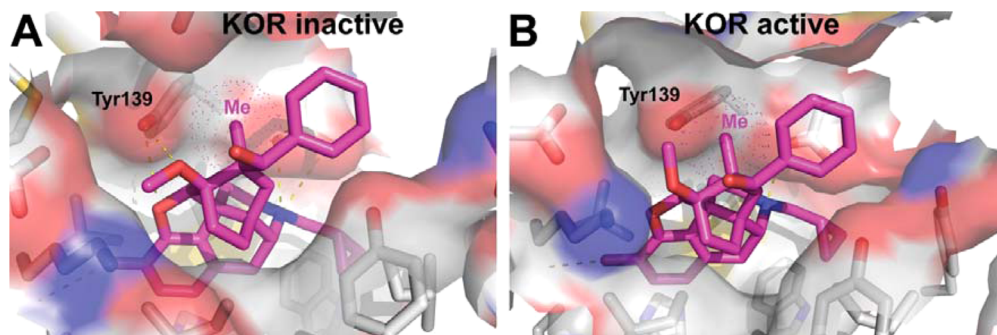


Figure 1. Proposed binding modes for **15a** (purple) in the models of inactive (A) and active (B) conformations of human KOR. The C7 β -methyl group of **15a** negatively interacts with Tyr139 in the active receptor conformation but not in the inactive one.

1H), 5.57 (d, 1H, $J = 12.0$ Hz), 5.33 (d, 1H, $J = 8.0$ Hz), 4.76 (d, 1H, 0.4H), 4.57–4.53 (m, 1.6H), 4.15–4.10 (m, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.42 (dt, 1H, $J_a = 12.0$ Hz, $J_b = 4.0$ Hz), 3.11–3.05 (dd, 1H, $J_a = 8.0$ Hz, $J_b = 4.0$ Hz), 2.88–2.83 (m, 1H), 2.43–2.35 (dt, 1H, $J_a = 12.0$ Hz, $J_b = 8.0$ Hz), 1.85–1.76 (m, 1H), 1.69–1.65 (m, 1H), 1.09–1.03 (m, 5H), 0.91–0.76 (m, 2H). ESIMS: m/z 436 ($M + H^+$, 100). In addition, 4.11 g of a slower running component, *N*-cyclopropylcarbonyl-7 α -formyl-7 β -methyl-6,14-endoethenotetrahydronorthebaine (4b), was afforded as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 9.54 (s, 0.5H), 9.45 (s, 0.5H), 6.69 (d, 1H, $J = 8.0$ Hz), 6.59 (d, 1H, $J = 8.0$ Hz), 6.14 (t, 1H), 5.57 (dd, 1H, $J_a = 12.0$ Hz, $J_b = 8.0$ Hz), 5.35 (d, 0.5H, $J = 4.0$ Hz), 4.93 (s, 1H), 4.80 (d, 0.5H, $J = 8.0$ Hz), 4.64 (dd, 1H, $J_a = 8.0$ Hz, $J_b = 4.0$ Hz), 4.15 (dd, 1H, $J_a = 8.0$ Hz, $J_b = 4.0$ Hz), 3.85 (s, 3H), 3.72 (2s, 3H), 3.49 (dt, 1H), 3.31–3.21 (m, 2H), 2.37–2.26 (dt, 0.5H), 2.27–2.15 (dt, 0.5H), 2.06–1.72 (m, 3H), 1.35 (s, 3H), 1.08 (m, 2H), 0.82 (m, 2H). At RT, the ^1H NMR spectra of this compound in $\text{DMSO}-d_6$ has two signals at δ 9.408 (s, 0.5H) and δ 9.375 (s, 0.5H) that coalesce when running the ^1H NMR experiment at 360 K. ESIMS: m/z 436 ($M + H^+$, 100).

***N*-Cyclopropylcarbonyl-7 α -formyl-7 β -methyl-6,14-endoethanotetrahydronorthebaine (11).** Aldehyde 4b (500 mg) was dissolved in 15 mL of EtOH. Into this solution was added 30 mg of 10% Pd on carbon. The mixture was shaken in a Parr hydrogenator under 100 psi of H_2 for 12 h. The mixture was filtered, and the solvents were removed under reduced pressure to yield 510 mg of 11 as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 9.70 (s, 0.6H), 9.69 (s, 0.4H), 6.76 (d, 1H, $J = 8.1$ Hz), 6.61 (d, 1H, $J = 8.1$ Hz), 4.9 (d, 0.4H, $J = 6.9$ Hz), 4.82 (s, 0.6H), 4.81 (s, 0.4H), 4.52 (dd, 0.6H, $J_a = 14$ Hz, $J_b = 5.7$ Hz), 4.34 (d, 0.6H, $J = 6.8$ Hz), 4.04 (dd, 0.4H, $J_a = 15$, $J_b = 6$ Hz), 3.89 (s, 3H), 3.48 (s, 1.8H), 3.46 (s, 1.2H), 3.34 (td, 0.4H, $J_a = 13.4$, $J_b = 3.2$ Hz), 3.05 (dd, 0.6H, $J_a = 18.5$ Hz, $J_b = 6.9$ Hz), 2.97 (dd, 0.4H, $J_a = 18.7$ Hz, $J_b = 7.2$ Hz), 2.87 (d, 0.6H, $J = 18.7$ Hz), 2.81 (td, 0.6H, $J_a = 13.7$, $J_b = 4.1$ Hz), 2.71 (d, 0.4H, $J = 18.8$ Hz), 2.42–2.37 (m, 1H), 2.27 (td, 0.4H, $J_a = 13.1$ Hz, $J_b = 5.7$ Hz), 2.16 (td, 0.6H, $J_a = 13.2$ Hz, $J_b = 5.8$ Hz), 1.80–1.60 (m, 3.6H), 1.5 (dd, 0.4H, $J_a = 13.7$ Hz, $J_b = 3.7$ Hz), 1.33–1.18 (m, 5H), 1.15–1.06 (m, 1H), 1.03–0.94 (m, 2H), 0.84–0.71 (m, 2H). ESIMS: m/z 438 ($M + H^+$, 100).

(1'S,5 α ,6R,7R,14 α)-1'-Phenyl-1'-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-7 β -methyl 17-cyclopropylcarbonyl-6,14-ethanomorphinan-7-yl)-methan-1'-ol (12a). General procedure A was followed using 515 mg of 11 to yield 336 mg of 12a as white crystals. ^1H NMR (400 MHz, CDCl_3) δ 7.36–7.23 (m, 5H), 6.78–6.75 (2d, 1H), 6.61–6.58 (2d, 1H), 5.06 (d, 0.55H, $J = 2.6$ Hz), 4.99 (d, 0.45H, $J = 2.6$ Hz), 4.91–4.87 (m, 1H), 4.51–4.46 (dd, 0.55H, $J_a = 5.4$ Hz, $J_b = 13.7$ Hz), 4.35–4.34 (d, 0.55H, $J = 6.8$ Hz), 4.03–3.98 (d, 0.45H, $J_a = 4.9$ Hz, $J_b = 13.5$ Hz), 3.92–3.914 (2s, 3H), 3.53 (s, 1.65H), 3.48 (s, 1.35H), 3.38–3.30 (dt, 0.55H, $J_a = 3.8$ Hz, $J_b = 8.6$ Hz), 3.11–3.04 (dd, 0.55H, $J_a = 6.9$ Hz, $J_b = 18.3$ Hz), 3.02–2.96 (dd, 0.45H, $J_a = 6.9$ Hz, $J_b = 18.5$ Hz), 2.92–2.88 (d, 0.55H, $J = 18.3$ Hz), 2.49–2.44 (m, 1H), 2.36–2.29 (dt, 0.45 Hz, $J_a = 5.6$ Hz, $J_b = 12.9$ Hz), 2.25–2.17 (dt, 0.55 Hz, $J_a = 6.0$ Hz, $J_b = 13.2$ Hz), 2.03–1.90 (m, 2H), 1.86–1.80 (m, 0.45 Hz), 1.76–1.51 (m, 6H), 1.10–0.69 (m, 7H). ESIMS: m/z 516 ($M + H^+$, 100).

(1'R,5 α ,6R,7R,14 α)-1'-Phenyl-1'-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-7 β -methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1'-ol (14a). General procedure B was followed using 473 mg of 12a to yield a clear residue after extraction. Crystallization from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ gave 133 mg of 14a as white crystals. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (m, 2H), 7.34–7.30 (m, 2H), 7.27–7.24 (m, 1H), 6.73 (d, 1H, $J = 8.4$ Hz), 6.57 (d, 1H, $J = 8.0$ Hz), 5.76 (s, 1H), 5.03 (s, 1H), 4.96 (s, 1H), 3.91 (s, 3H), 3.64 (s, 3H), 3.01–2.94 (m, 2H), 2.57 (d, 1H, $J = 6.8$ Hz), 2.29 (dd, 1H, $J_a = 6.8$ Hz, $J_b = 18.3$ Hz), 2.24–2.20 (m, 3H), 1.95 (dd, 1H, $J_a = 4$ Hz, $J_b = 14.3$ Hz), 1.90–1.77 (m, 2H), 1.60–1.52 (m, 2H), 1.40–1.28 (m, 4H), 0.95 (m, 1H), 0.68 (m, 1H), 0.51–0.39 (m, 2H), 0.08–0.01 (m, 2H). ESIMS: m/z 502 ($M + H^+$, 100).

(1'R,5 α ,6R,7R,14 α)-1'-Phenyl-1'-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7 β -methyl 17-cyclopropylmethyl-6,14-ethanomorphinan-7-yl)-methan-1'-ol (15a). General procedure C was followed using 133 mg of 14 to yield 75 mg of 15a as a white

solid. ^1H NMR (400 MHz, CDCl_3) δ 7.49–7.42 (m, 2H), 7.35–7.28 (m, 2H), 7.28–7.20 (m, 1H), 6.61 (d, 1H, $J = 8.0$ Hz), 6.47 (d, 1H, $J = 8.0$ Hz), 5.98 (s, 1H), 5.05 (s, 1H), 4.95 (d, 1H, $J = 1.6$ Hz), 3.59 (s, 3H), 2.98 (d, 1H, $J = 6.4$ Hz), 2.93 (d, 1H, $J = 18.3$ Hz), 2.63–2.50 (m, 1H), 2.32–2.13 (m, 5H), 1.95 (dd, 1H, $J_a = 14.2$ Hz, $J_b = 3.9$ Hz), 1.89–1.71 (m, 2H), 1.59–1.44 (m, 2H), 1.35–1.21 (m, 4H), 0.97–0.81 (m, 1H), 0.75–0.60 (m, 1H), 0.52–0.36 (m, 2H), 0.10–0.03 (m, 2H). ESIMS: m/z 488 ($M + H^+$, 100).

Molecular Modeling. We used the crystal structure of the human KOR (PDB ID: 4djh) together with our previous active state models.²³ Compound 15a was built, and the low-energy conformation was then subjected to automated rigid docking implemented in QUANTA (Accelrys Inc.).

■ ASSOCIATED CONTENT

Supporting Information

Full characterization of final compounds; microanalysis and HPLC; pharmacological methods. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b00130.

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Notes

The authors declare the following competing financial interest(s): Subsequent to preparation of the manuscript the compounds disclosed have been licensed to a biopharmaceutical company.

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■ ABBREVIATIONS USED

MOP receptor, mu opioid receptor; DOP receptor, delta opioid receptor; KOP receptor, kappa opioid receptor; NOP receptor, nociceptin opioid peptide receptor; EKC, ethylketocyclazocine; N/OFOQ, nociceptin/orphanin FQ

■ REFERENCES

- (1) Husbands, S. M. Buprenorphine and related orvinols. *Research and Development of Opioid-Related Ligands*; ACS Symposium Series: New York, 2013; Vol. 1131, pp 127–144.
- (2) McLellan, A. T.; Lewis, D. C.; O'Brien, C. P.; Kleber, H. D. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *J. Am. Med. Assoc.* **2000**, *284*, 1689–1695.
- (3) Rodriguez-Arias, M.; Aguilar, M. A.; Manzanedo, C.; Minarro, J. Preclinical evidence of new opioid modulators for the treatment of addiction. *Expert Opin. Invest. Drugs* **2010**, *19*, 977–994.
- (4) Cordery, S. F.; Taverner, A.; Ridzwan, I. E.; Guy, R. H.; Delgado-Charro, M. B.; Husbands, S. M.; Bailey, C. P. A non-rewarding, non-aversive buprenorphine/naltrexone combination attenuates drug-

primed reinstatement to cocaine and morphine in rats in a conditioned place preference paradigm. *Addict. Biol.* **2014**, *19*, 575–586.

(5) Taverner, A.; Cordery, S.; Husbands, S. M.; Guy, R. H.; Delgado-Charro, B. M.; Bailey, C. P. Transdermal delivery of a buprenorphine/naltrexone combination for the treatment of polydrug abuse. *Pharmacol. Rep.* **2011**, *63*, 257–257.

(6) Lee, K. O.; Akil, H.; Woods, J. H.; Traynor, J. R. Differential binding properties of oripavines at cloned mu- and delta-opioid receptors. *Eur. J. Pharmacol.* **1999**, *378*, 323–330.

(7) Bloms-Funke, P.; Gillen, C.; Schuettler, A. J.; Wnendt, S. Agonistic effects of the opioid buprenorphine on the nociceptin/OFQ receptor. *Peptides* **2000**, *21*, 1141–1146.

(8) Rothman, R. B.; Gorelick, D. A.; Heishman, S. J.; Eichmiller, P. R.; Hill, B. H.; Norbeck, J.; Liberto, J. G. An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence. *J. Subst. Abuse Treat.* **2000**, *18*, 277–281.

(9) Gerra, G.; Fantoma, A.; Zaimovic, A. Naltrexone and buprenorphine combination in the treatment of opioid dependence. *J. Psychopharmacol.* **2006**, *20*, 806–814.

(10) Hans, G. H. Buprenorphine in the treatment of neuropathic pain. *Research and Development of Opioid-Related Ligands*; ACS Symposium Series: New York, 2013; Vol. 1131, pp 103–123.

(11) McCann, D. J. Potential of buprenorphine/naltrexone in treating polydrug addiction and co-occurring psychiatric disorders. *Clin. Pharmacol. Ther.* **2008**, *83*, 627–630.

(12) Cremeans, C. M.; Gruley, E.; Kyle, D. J.; Ko, M.-C. Roles of mu-opioid receptors and nociceptin/orphanin FQ peptide receptors in buprenorphine-induced physiological responses in primates. *J. Pharmacol. Exp. Ther.* **2012**, *343*, 72–81.

(13) Sukhtankar, D. D.; Zaveri, N. T.; Husbands, S. M.; Ko, M.-C. Effects of spinally administered bifunctional NOP/MOP ligands in mouse models of neuropathic and inflammatory pain. *J. Pharmacol. Exp. Ther.* **2013**, *346*, 11–22.

(14) Greedy, B. M.; Bradbury, F.; Thomas, M. P.; Grivas, K.; Cami-Kobeci, G.; Archambeau, A.; Bosse, K.; Clark, M. J.; Aceto, M.; Lewis, J. W.; Traynor, J. R.; Husbands, S. M. Orvinols with mixed kappa/mu opioid receptor agonist activity. *J. Med. Chem.* **2013**, *56*, 3207–3216.

(15) Kumar, V.; Ridzwan, I. E.; Grivas, K.; Lewis, J. W.; Clark, M. J.; Meurice, C.; Jimenez-Gomez, C.; Pogozheva, I.; Mosberg, H.; Traynor, J. R.; Husbands, S. M. Selectively promiscuous opioid ligands: discovery of high affinity/low efficacy opioid ligands with substantial nociceptin opioid peptide receptor affinity. *J. Med. Chem.* **2014**, *57*, 4049–4057.

(16) Bentley, K. W.; Hardy, D. G.; Meek, B.; Taylor, J. B.; Brown, J. J.; Morton, G. O. Novel analgesics and molecular rearrangements in the morphine-thebaine group. Part X. Further acid-catalysed rearrangements of alcohols in the 6,14-endo-ethenotetrahydrothebaine series. *J. Chem. Soc. C* **1969**, 2229–2232.

(17) Coop, A.; Grivas, K.; Husbands, S.; Lewis, J. W. Methylation of the enolates of thevinone and some analogs. *Tetrahedron* **1995**, *51*, 9681–9698.

(18) Husbands, S. M.; Lewis, J. W. Morphinan cyclic imines and pyrrolidines containing a constrained phenyl group: high affinity opioid agonists. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2969–2974.

(19) Lewis, J. W.; Readhead, M. J.; Selby, I. A.; Smith, A. C. B.; Young, C. A. Novel analgesics and molecular rearrangements in the morphine-thebaine group. Part XIX. Further Diels–Alder adducts of thebaine. *J. Chem. Soc. C* **1971**, 1158–1161.

(20) Barton, J. W.; Coop, A.; Lewis, J. W. Diels–Alder Reactions of thebaines with cycloalkenones—lithium tetrafluoroborate as a novel Diels–Alder catalyst. *Tetrahedron Lett.* **1993**, *34*, 6777–6778.

(21) Spagnolo, B.; Calo, G.; Polgar, W. E.; Jiang, F.; Olsen, C. M.; Berzetei-Gurske, I.; Khroyan, T. V.; Husbands, S. M.; Lewis, J. W.; Toll, L.; Zaveri, N. T. Activities of mixed NOP and mu-opioid receptor ligands. *Br. J. Pharmacol.* **2008**, *153*, 609–619.

(22) Husbands, S. M.; Neilan, C. L.; Broadbear, J.; Grundt, P.; Breeden, S.; Aceto, M. D.; Woods, J. H.; Lewis, J. W.; Traynor, J. R. BU74, a complex oripavine derivative with potent kappa opioid

receptor agonism and delayed opioid antagonism. *Eur. J. Pharmacol.* **2005**, *509*, 117–125.

(23) Anand, J. P.; Purington, L. C.; Pogozheva, I. D.; Traynor, J. R.; Mosberg, H. I. Modulation of opioid receptor ligand affinity and efficacy using active and inactive state receptor models. *Chem. Biol. Drug Des.* **2012**, *80*, 763–770.

(24) Traynor, J. R.; Nahorski, S. R. Modulation by mu-opioid agonists of guanosine-5'-O-(3-S-35 thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. *Mol. Pharmacol.* **1995**, *47*, 848–854.

(25) Wu, H.; Wacker, D.; Mileni, M.; Katritch, V.; Han, G. W.; Vardy, E.; Liu, W.; Thompson, A. A.; Huang, X.-P.; Carroll, F. I.; Mascarella, S. W.; Westkaemper, R. B.; Mosier, P. D.; Roth, B. L.; Cherezov, V.; Stevens, R. C. Structure of the human kappa-opioid receptor in complex with JDTic. *Nature* **2012**, *485*, 327–332.

(26) Lewis, J. W.; Husbands, S. M. The orvinols and related opioids—high affinity ligands with diverse efficacy profiles. *Curr. Pharm. Des.* **2004**, *10*, 717–732.

(27) Husbands, S. M.; Lewis, J. W. Structural determinants of efficacy for kappa opioid receptors in the orvinol series: 7,7-spiro analogues of buprenorphine. *J. Med. Chem.* **2000**, *43*, 139–141.

(28) Zaveri, N.; Polgar, W. E.; Olsen, C. M.; Kelson, A. B.; Grundt, P.; Lewis, J. W.; Toll, L. Characterization of opiates, neuroleptics, and synthetic analogs at ORL1 and opioid receptors. *Eur. J. Pharmacol.* **2001**, *428*, 29–36.

(29) Lutfy, K.; Eitan, S.; Bryant, C. D.; Yang, Y. C.; Saliminejad, N.; Walwyn, W.; Kieffer, B. L.; Takeshima, H.; Carroll, F. I.; Maidment, N. T.; Evans, C. J. Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. *J. Neurosci.* **2003**, *23*, 10331–10337.

(30) Lutfy, K.; Cowan, A. Buprenorphine: a unique drug with complex pharmacology. *Curr. Neuropharmacol.* **2004**, *2*, 395–402.

(31) Cami-Kobeci, G.; Polgar, W. E.; Khroyan, T. V.; Toll, L.; Husbands, S. M. Structural determinants of opioid and NOP receptor activity in derivatives of buprenorphine. *J. Med. Chem.* **2011**, *54*, 6531–6537.

(32) Khroyan, T. V.; Polgar, W. E.; Cami-Kobeci, G.; Husbands, S. M.; Zaveri, N. T.; Toll, L. The first universal opioid ligand, (2S)-2-[(SR,6R,7R,14S)-N-cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylpentan-2-ol (BU08028): characterization of the in vitro profile and in vivo behavioral effects in mouse models of acute pain and cocaine-induced reward. *J. Pharmacol. Exp. Ther.* **2011**, *336*, 952–961.

(33) Yu, G.; Yan, L.-D.; Li, Y.-L.; Wen, Q.; Dong, H.-J.; Gong, Z.-H. TH-030418: a potent long-acting opioid analgesic with low dependence liability. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2011**, *384*, 125–131.